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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Ex parte
WERNER OBEREGGER, OKPONANABOFA ERADIRI, FANG ZHOU, and PAUL MAES

Appeal 2008-0304
Application 10/507,525
Technology Center 1600

Decided: July 31, 2008

Before TONI R. SCHEINER, LORA M. GREEN, and RICHARD M. LEBOVITZ, *Administrative Patent Judges.*

SCHEINER, *Administrative Patent Judge.*

DECISION ON APPEAL

This is an appeal under 35 U.S.C. § 134 from the final rejection of claims 155-172, all the claims remaining in the application. We have jurisdiction under 35 U.S.C. § 6(b).

BACKGROUND

"Bupropion hydrochloride is commercially available as an immediate release form (Wellbutrin®) and a sustained release form (Wellbutrin® SR and Zyban®). Both Wellbutrin® SR and Zyban® are chemically and pharmaceutically identical" (Spec. ¶ 2). "Wellbutrin® and Wellbutrin® SR are used for the management of depression. Zyban® has been approved as an aid to patients wanting to quit smoking" (Spec. ¶ 4).

"Wellbutrin®, the immediate release formulation of bupropion, is dosed three times a day" (Spec. ¶ 4). "The immediate release formulation results in more than a 75% release of bupropion . . . in about 45 minutes, and one of the major side effects of bupropion has been the incidence of seizures, which in part appears to be strongly associated with the immediate release of the bupropion into the system" (*id.*). As a result, "sustained release products were developed to avoid the incidence of seizures. The sustained release products are dosed twice daily" (*id.*).

"In general, patient compliance is a problem with medications that require a multiple dosing regimen and is especially problematic with depressed individuals. While sustained release formulations have simplified the dosing regimen and increased patient compliance, there is still room for further simplifying the dosing regimen" (Spec. ¶ 5). "The present invention relates to a modified-release tablet of . . . bupropion hydrochloride . . . [that] allow[s] for a once daily administration regimen, is bioequivalent to the commercially available prior art tablets and do[es] not exhibit a food effect" (Spec. ¶ 17).

STATEMENT OF THE CASE

Claims 155-172 are pending and on appeal. Claims 155, 156, 165, and 172 are representative:

155. A modified-release tablet suitable for use in once-daily administration of bupropion treatment regimen in patients in need of such bupropion administration wherein said modified-release tablet is bioequivalent to Wellbutrin® or Zyban/Wellbutrin® SR tablets over a 24 hour period when said modified-release tablet is administered in a once-a-day bupropion treatment regimen to a patient in need of such bupropion administration.

156. The modified release tablet of claim 155 which does not exhibit any food effects.

165. The modified-release tablet of claim 155 which when administered in a once-daily bupropion treatment regimen to a patient in need of treatment provides a C_{max} for bupropion ranging from about 60ng/ml at between 3 hours and 8 hours (T_{max}), and $AUC_{(0\text{-}inf)}$ for bupropion ranging from about 800 ng.hr/ml to about 2850 ng.hr/ml[.]

172. The modified-release tablet of claim 155 which comprises:
(i) a bupropion containing core;
(ii) a polymeric control release coating substantially surrounding said core; and
(iii) a polymeric moisture barrier substantially surrounding said polymeric release coating;
wherein the polymeric constituents and t[h]e amounts thereof contained in said control-release coating and said moisture barrier are selected such that a modified-release tablet is obtained that is bioequivalent to Wellbutrin® or Zyban/Wellbutrin® SR tablets over a 24 hour period.

The claims stand rejected as follows:

I. Claims 155-172 under 35 U.S.C. § 112, first paragraph, as lacking adequate written descriptive support.

II. Claims 155-172 under 35 U.S.C. § 112, second paragraph, as indefinite.

III. Claims 155, 156, 159-162, 165-167, and 169-171 under 35 U.S.C. § 102(e), as anticipated by Li (Patent Application US 2003/0161874 A1, published August 28, 2003).

FINDINGS OF FACT (**FF**)

FF 1. Bupropion hydrochloride is commercially available as an immediate release form sold under the tradename Wellbutrin®, and as a sustained release form sold under the tradenames Wellbutrin® SR and Zyban® (Spec. ¶ 2).

FF 2. Wellbutrin®, the immediate release form, is dosed three times a day. Wellbutrin® SR and Zyban® are chemically and pharmaceutically identical sustained release formulations, and are dosed twice a day (Spec. ¶ 4).

FF 3. In Example 1, the Specification describes six "modified-release" tablet formulations of bupropion hydrochloride: three different 150 mg dosage forms (A, B, and C), and three different 300 mg dosage forms (A', B', and C') (Spec. ¶¶ 98-110).

FF 4. Each of the six formulations has a "core" (Spec. Table 1) coated with a "control-releasing coat" (Spec. Table 3), which is coated in turn with a "moisture barrier" (Spec. Table 5).

FF 5. The Specification teaches that the core, in addition to bupropion hydrochloride, contains binders, lubricants, and "other conventional inert excipients" (Spec. ¶ 67), that "[t]he control-releasing coat is a semi-permeable coat comprising a water-insoluble, water-permeable film-forming polymer, a plasticizer and a water-soluble polymer" (Spec. ¶ 76), and that

"[t]he moisture barrier . . . comprises an enteric and/or acrylic polymer, [and] a permeation enhancer" (Spec. ¶ 85).

FF 6. The Specification lists a number of ingredients suitable for the various components of the core, the control-releasing coat, and the moisture barrier (Spec. ¶¶ 66-92), and indicates that the ingredients may be present in varying amounts and relative proportions (*id.*).

FF 7. As shown in Tables 1, 3, and 5, all six of the exemplified modified-release formulations contain the same ingredients, in the same layers, but the amounts and relative proportions of the ingredients in the layers vary.

FF 8. The mean percent release of the total bupropion hydrochloride content from each of the six modified-release formulations is shown in Table 7 of the Specification.

FF 9. Of the six modified-release formulations, "C and C' for the 150 mg and 300 mg dosage forms were selected for all further tests" (Spec. ¶ 110), including stability (Spec. ¶¶ 111-113), dosage strength equivalency of the 150 mg and 300 mg modified-release forms (Spec. ¶¶ 123-130), and a fasting and food-effect comparative bioavailability study of the bupropion hydrochloride modified-release 150 mg tablets of Example 1 and Zyban® 150 mg tablets (Spec. ¶¶ 131-140).

FF 10. According to the Specification, the results of the latter test "show that the bioavailability of bupropion . . . does not show a food effect" (Spec. ¶ 140).

FF 11. Formulation C' was used in a "comparative bioavailability study of a once-daily bupropion hydrochloride 300 mg modified-release tablet of the invention versus the immediate release thrice daily Wellbutrin® 100 mg

tablets" (Spec. ¶ 149). According to the Specification, the results showed "that a 300 mg dosage strength modified-release tablet of the invention administered once daily is bioequivalent to the 100 mg dosage strength immediate release Wellbutrin® administered thrice daily" (Spec. ¶ 156).

FF 12. A similar study showed "that a 300 mg (q.d.) [once daily] dosage strength modified-release bupropion hydrochloride tablet of the invention is bioequivalent to the 150 mg b.i.d. [twice daily] sustained-release commercially available prior art Zyban® tablet" (Spec. ¶ 164).

FF 13. According to the Specification,

> [t]he term "bioequivalent" means the absence of a significant difference in the rate and extent to which the active ingredient or active moiety in pharmaceutical equivalents or pharmaceutical alternatives becomes available at the site of drug action when administered at the same molar dose under similar conditions in an appropriately designed study. Where there is an intentional difference in rate (e.g., in certain extended release dosage forms), certain pharmaceutical equivalents or alternatives may be considered bioequivalent if there is no significant difference in the extent to which the active ingredient or moiety from each product becomes available at the site of drug action. This applies only if the difference in the rate at which the active ingredient or moiety becomes available at the site of drug action is intentional and is reflected in the proposed labeling, is not essential to the attainment of effective body drug concentrations on chronic use, and is considered medically insignificant for the drug.

(Spec. ¶ 16.)

FF 14. Further according to the Specification, bioequivalence is "evidenced by the fact that the 90% CI of the ratio of the geometric means for the $AUC_{0\text{-}inf}$ (and the $AUC_{0\text{-}t}$ when appropriate) and C_{max} . . . fall within the FDA suggested limits of 80-125%" (Spec. ¶¶ 140, 148).

FF 15. Thus, as the term is used in the Specification, two formulations are "bioequivalent" if one can be 90% confident that at least the ratio of the geometric means of the $AUC_{0\text{-}inf}$ for the two formulations, and the ratio of the geometric means for C_{max} for the two formulations, fall within the confidence limits of 80-125%.

FF 16. A formulation does not show a "food effect" if its bioavailability is unaffected by the presence or absence of food, i.e., if its bioavailability is unchanged under fasting and fed conditions (Spec. ¶ 140, 148).

FF 17. Li describes a bupropion hydrochloride formulation said to "provide 24-hour efficacy with once daily dosing, with less than 50% of the drug released at 10 hours. Therapeutic plasma levels are maintained from 12 to 24 hours. The usual dosage range is 75-450 mg" (Li ¶ 28).

FF 18. According to Li, "[t]he formulation functions by membrane-controlled extended-release in a pH dependent manner. The bupropion release rate has been improved by the introduction of two types of film coated active pellets that release the drug at different pH resulting in novel dissolution profiles" (Li ¶ 26). "Enteric coated pellets" and "sustained-release pellets" may be combined in various proportions to form a two-component controlled release formulation. The two types of pellets may further be combined with an immediate release form of bupropion hydrochloride to form a three-component controlled release formulation (Li ¶¶ 35-56).

FF 19. Example 1 of Li describes a two-component "controlled release 150 mg oral bupropion dosage form" (Li ¶¶ 77-83).

FF 20. "Two panels of seven patients were randomly assigned to receive either the bupropion formulation . . . [of Example 1] or ZYBAN® in an open, randomized single dose study. Blood samples were collected . . . and analyzed" (Li ¶ 89). The mean $AUC_{0\text{-}inf}$ of the Example 1 bupropion formulation was 832 ng.hr/ml (Li ¶ 90; Table 3), and "[t]he mean C_{max} value of the Example 1 bupropion formulation was [54.2 ng/ml] about one-half of that for Zyban® . . . The relative bioavailability of the Example 1 formulation to Zyban® was 40% in terms of C_{max} and 80% in terms of $AUC_{0\text{-}inf}$ ratio" (Li ¶ 90; Table 3).

DISCUSSION

Written Description

The Examiner rejected claims 155-172 under 35 U.S.C. § 112, first paragraph, as lacking adequate written descriptive support "based on lack of possession of the full scope of the genus [of] control-release tablets encompassed by the claims based on the limited disclosure of 2 species of control-release tablets" (Ans. 9).

The Examiner's position is essentially that the Specification exemplifies only two formulations with the claimed functional properties, and these "claimed functional properties are achieved from specific formulations that contain specific structures, such as dosage core with coating layers that comprise specific ratios of film forming polymers" (Ans. 3), thus, the specific "structure which makes up the formulation must be clearly and positively specified in order to place one of skill in the art in possession of the claimed tablets with the desired properties" (*id.*). The Examiner argues that "[t]his is . . . evident by the comparison data [in

Example 8] showing formulations with different structure that resulted in different functional properties" (*id.*).

> Appellants concede that
>
> the subject specification only exemplifies 2 bioequivalent bupropion tablet formulations that respectively contain 150 or 300 mg of bupropion, and which each further respectively comprise (i) a control-release coating that substantially controls bupropion drug release as well as (ii) a moisture barrier coating that impedes moisture retention wherein both coatings are comprised of specific polymeric constituents comprised in specific weight percentages

(App. Br. 24), but argue that one of skill in the art would understand that Appellants were in possession of a genus of "modified-release tablets which are bioequivalent to Wellbutrin® or Zyban/Wellbutrin® . . . [and which are] not limited to modified release tablets comprising the specific modified release coating and the amounts thereof contained in the two exemplified modified-release tablets" (App. Br. 27).

Appellants point out that the Specification describes "a wide range of different film-forming polymers, plasticizers and water soluble polymers that may be substituted for those contained in the exemplified control-release coatings" (App. Br. 26), and "teaches in paragraph [0082] that 'the permeability of the control-release coating may be varied by altering the ratio of the water-insoluble, water permeable film-forming polymer: water soluble polymer and/or the amount of coating applied to the tablet core'" (*id.*). Appellants note that "it can be seen from Table 3 of this application that the exemplified 150 and 300 mg tablets, while both bioequivalent,

contain different ratios of polymers in the control-release coating and further contain different amount[s] of such control-release coating" (App. Br. 28).

As framed by Appellants and the Examiner, then, the issue raised by this appeal is whether the two species of once a day bupropion formulations bioequivalent to Wellbutrin® or Zyban/Wellbutrin® SR described in the Specification are representative of the full scope of the claimed genus, or whether the written description is only adequate to support claims limited to the two exemplified modified-release tablets. However, in our view, the real issue raised by this appeal is whether the Specification's written description is adequate to support claims to a genus that encompasses all once a day bupropion formulations bioequivalent to Wellbutrin® or Zyban/Wellbutrin® SR, no matter what their structure is.

The first paragraph of § 112 does not require a description of the complete structure of every species within a chemical genus. *See Utter v. Hiraga*, 845 F.2d 993, 998 (Fed. Cir. 1988) ("A specification may, within the meaning of 35 U.S.C. § 112, ¶ 1, contain a written description of a broadly claimed invention without describing all species that claim encompasses."). In *University of California v. Eli Lilly and Co.*, 119 F.3d 1559, 1569 (Fed. Cir. 1997), the court explained that "[a] description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus." This requirement for a representative number of species falling within the scope of a genus applies to inventions other than DNA as

well. *See University of Rochester v. G.D. Searle & Co., Inc.*, 358 F.3d 916, 927 (Fed. Cir. 2004).

The only bupropion hydrochloride formulations described in the Specification have certain structural features in common: a bupropion containing core, a polymeric control release coating surrounding the core (which comprises a water-insoluble, water-permeable film-forming polymer, a plasticizer and a water-soluble polymer), and a polymeric moisture barrier (which comprises an enteric and/or acrylic polymer, and a permeation enhancer surrounding the release coating) (**FF 3-5**). However, according to the Specification, the exact constituents of these coatings can be selected from the various polymers and plasticizers listed in the Specification, and can vary in their amounts and relative proportions (**FF 6**). Therefore, we find that the Specification adequately describes the genus of once a day bupropion formulations bioequivalent to Wellbutrin® or Zyban/Wellbutrin® SR with the common structural features disclosed in the Specification, without regard to exact constituents, their amount, or proportion (**FF 5**, **6**). Nevertheless, we find that the Specification does not establish that Appellants were in possession of the larger genus of once a day bupropion formulations bioequivalent to Wellbutrin® or Zyban/Wellbutrin® SR, that do not have at least those structural features common to the exemplified formulations.

Accordingly, the rejection of claims 155-171 under 35 U.S.C. § 112, first paragraph, is affirmed.

Indefiniteness

The Examiner rejected claims 155-172 under 35 U.S.C. § 112, second paragraph, as indefinite.

There is no dispute that the tradenames Wellbutrin® and Zyban/ Wellbutrin® are used as limitations in the claims to identify particular commercially available formulations against which the relative pharmacokinetic properties of the claimed formulations are measured. *See Ex parte Simpson*, 218 USPQ 1020 (BPAI 1982).

According to the Examiner, the trade names Wellbutrin® and Zyban/Wellbutrin® SR in the claims are "used to identify/describe bupropion and, accordingly, the identification/description is indefinite . . . [as] the exact ingredients of Wellbutrin® and Zyban/Wellbutrin® [SR] . . . can change over time" (Ans. 4).

Appellants argue that "the Examiner's concern as to the possibility of change of the recited bupropion formulations is misplaced since the FDA has approved the recited bupropion formulations for therapeutic usage in large part based on their PK parameters" (App. Br. 10), i.e., the "AUC 0-inf, AUC 0-t and C_{max} values (PK parameters) as set forth in the Table and Figures of this application" (*id.*). "Accordingly, even assuming arguendo that such FDA approved, commercially available Zyban/Wellbutrin® SR or Wellbutrin® formulations were later modified . . . [the] meaning of the claims would still be clear" (*id.*). Appellants contend that "the instant claims are directed to bioequivalence to the pharmacokinetic parameters of the Wellbutrin[®] and Zyban/Wellbutrin[®] SR products . . . [and] [t]hose

pharmacokinetic parameters are set forth in the specification and therefore are not subject to change" (App. Br. 11).

This argument is not persuasive. If, as Appellants contend, the relevant "pharmacokinetic parameters are set forth in the specification and therefore are not subject to change" (App. Br. 11), but the composition of Zyban/Wellbutrin® SR or Wellbutrin® *is* subject to change (however unlikely), we cannot agree with Appellants that "defining the subject modified release tablets by reference to these tradenames actually more precisely defines the scope of the claimed invention" (App. Br. 11).

The rejection of claims 155-172 under 35 U.S.C. § 112, second paragraph, as indefinite is affirmed.

Anticipation by Li

Claims 155, 156, 159-162, 165-167, and 169-171 stand rejected under 35 U.S.C. § 102(e) as anticipated by Li.

According to the Examiner, "Li discloses a sustained release formulation in a form of a tablet or capsule comprising bupropion hydrochloride for once a day administration" that "does not exhibit any food effects" (Ans. 5), where "the amount of bupropion is 75-450 mg" (*id.*).

Appellants note that all the claims on appeal "are directed to a modified-release tablet containing bupropion suitable for once a day administration that is 'bioequivalent' to the previous commercially available and FDA approved bupropion formulations, i.e., Wellbutrin® and Zyban/Wellbutrin® SR" (App. Br. 42).[1] Appellants further note that claims

[1] We note that the claims on appeal actually require bioequivalence to Wellbutrin® **or** Zyban/Wellbutrin® SR.

156 and 159 require a modified release tablet which does not exhibit any food effects (App. Br. 46).

The principal issue raised by this rejection, then, is whether Li's once a day sustained release bupropion hydrochloride formulation is bioequivalent to Wellbutrin® or Zyban/Wellbutrin® SR, as the term "bioequivalent" is used in the present Specification. A secondary issue is whether the evidence supports the Examiner's finding that Li's once a day formulation does not exhibit any food effects.

Appellants contend that "[t]he present specification is clear that two different bupropion formulations are bioequivalent only if the 90% confidence interval (CI) of the geometric means of the C_{max} and AUC 0-t or AUC 0-inf parameters (PK parameters) range from 80% to 125%" (App. Br. 42).

According to Appellants, the data in Li's Table 3 shows "that the geometric mean ratio of C_{max} for . . . [the Li] formulation and that for Zyban[®] is 0.40 and the geometric mean of the AUC 0-inf values for the Li formulation and Zyban[®] is 0.80" (App. Br. 44), which "indicates that these formulations are not bioequivalent since these means do not range from 80-125%" (*id.*).

With respect to claims 156 and 159, Appellants contend that "the Li application does not contain any data that would allow a skilled artisan to conclude that their formulation is free of a food effect" (App. Br. 46).

In response, the Examiner contends that Li's formulation "must be 'bioequivalent'" because it has "the same structural elements required by the claims that results in the claimed properties, such as a C_{max} for bupropion at

about 8 hours (T_{max}) . . . [of] 54.2 ng, and [an] $AUC_{0\text{-}inf}$ . . . [of] 832 ng.hr/ml" (Ans. 13), and by the same token, must inherently exhibit no food effects (Ans. 5, 13).

The Examiner does not explain what is meant by "structural elements," but it is true that the values of C_{max} and $AUC_{0\text{-}inf}$ for the formulation of Li's Example 1 (54.2 ng/ml at about 8 hrs and 832 ng.hr/ml, respectively) are similar to values required for some of the presently claimed modified-release tablets (claim 165, for example, requires a C_{max} of 60 ng/ml at between 3 hours and 8 hours, and an $AUC_{0\text{-}inf}$ from about 800 to about 2850 ng.hr/ml) (**FF 20**). However, Li also reports that the ratio of geometric means for C_{max} is 0.40 (40%). Indeed, Li observes that "[t]he relative bioavailability of the Example 1 formulation to Zyban® was 40% in terms of C_{max}" (Li ¶ 90; **FF 20**).

While limitations from the Specification are not to be read into a claim, "[i]t is entirely proper to use the specification to interpret what . . . [is] meant by a word or a phrase in the claim." *E.I. Du Pont de Nemours & Co. v. Phillips Petroleum Co.*, 849 F.2d 1430, 1433 (Fed. Cir. 1988). *See also In re Morris*, 127 F.3d 1048, 1054 (Fed. Cir. 1997). As discussed above, the Specification indicates that the bioequivalence of two different formulations of the same drug is "evidenced by the fact that the 90% CI of the ratio of the geometric means for the $AUC_{0\text{-}inf}$ . . . and C_{max} . . . fall within the FDA suggested limits of 80-125%" (Spec. ¶¶ 140, 148; FF **13**, **14**).

The Examiner has not explained how the 90% CI of the ratio of geometric means of C_{max} for Li's formulation and Zyban® (40%) could fall

within 80-125%. Having nothing further from the Examiner on this point, we are left with an inadequate factual basis from which to conclude that Li's once a day formulation is bioequivalent to Zyban/Wellbutrin® SR or Wellbutrin®, or that Li's formulation does not exhibit food effects.

The rejection of claims 155, 156, 159-162, 165-167, and 169-171 under 35 U.S.C. § 102(e), as anticipated by Li is reversed.

SUMMARY

The rejection of claims 155-172 under 35 U.S.C. § 112, first paragraph, as lacking adequate written descriptive support is affirmed.

The rejection of claims 155-172 under 35 U.S.C. § 112, second paragraph as indefinite is affirmed.

The rejection of claims 155, 156, 159-162, 165-167, and 169-171 under 35 U.S.C. § 102(e), as anticipated by Li is reversed.

No time period for taking any subsequent action in connection with this appeal may be extended under 37 C.F.R. § 1.136(a)(1)(iv)(2006).

AFFIRMED

clj

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